Appeal No. 15-1871

In the United States Court of Appeals for the Federal Circuit

APOTEX INC.,

Appellant,

v.

WYETH LLC,

Appellee.

On Appeal From the United States Patent and Trademark Office, Patent Trial and Appeal Board, No. IPR2014-00115

BRIEF OF APPELLEE WYETH LLC

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CERTIFICATE OF INTEREST

Pursuant to Federal Circuit Rule 47.4, undersigned counsel for Appellee certifies the following:

1. The full name of the party represented by me is Wyeth LLC.

2. With respect to the name of the real party in interest represented by me, as well as any parent corporations and publicly-held companies that own 10 percent or more of the stock of the party represented by me, I hereby state as follows:

> Wyeth LLC, a Delaware limited liability company having a place of business at 235 East 42nd Street, New York, New York 10017, is the owner of the entire interest in U.S. Patent No. 7,879,828 ("the '828 patent"). PF PRISM, C.V., a limited partnership (commanditaire vennootschap) organized and existing under the laws of the Netherlands and having offices at Blaak 40 basement, 3011 TA, Rotterdam, Netherlands, took an exclusive license in the '828 patent. Thereafter, PF PRISM C.V. contributed its rights under the exclusive license to Pfizer Pharmaceuticals LLC, a Delaware limited liability company having a place of business at Bo. Carmelitas, Road 689, Km 1.9, Vega Baja, Puerto Rico 00693. Wyeth LLC, PF PRISM C.V., and Pfizer Pharmaceuticals LLC are wholly-owned, directly or indirectly, by Pfizer Inc., a publicly-traded company. Pfizer Inc. has no parent corporation and no publicly held corporation owns 10% or more of its stock.

3. The following attorneys appeared for Appellees in proceedings in the trial below or are expected to appear in this Court: of Williams & Connolly LLP: Stanley E. Fisher, David I. Berl, Thomas H. L. Selby, Adam D. Harber, Galina I. Fomenkova, Sara K. Creighton, David Kiernan, and Christopher C. Kennedy (no longer affiliated with Williams & Connolly LLP).

/s/ *David I. Berl*
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JANUARY 25, 2016

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STATEMENT OF RELATED CASES

The ’828 patent that is the subject of this appeal has been asserted in the following pending litigations: *Pfizer Inc. et al.* v. *Mylan Inc. et al.*, No. 15-cv-00026-SLR (D. Del.); *Pfizer Inc. et al.* v. *Mylan Inc. et al.*, No. 1:15-cv-00004-IMK (N.D. W. Va.); *Pfizer Inc. et al.* v. *Mylan Inc. et al.*, No. 1:15-cv-00960-SLR (D. Del.); and *Pfizer Inc. et al.* v. *Mylan Inc. et al.*, No. 1:15-cv-188-IMK (N.D. W. Va.). The other related cases cited by Appellant are no longer pending.

STATEMENT OF THE ISSUE

Whether substantial evidence supports the Board’s rejection of Apotex’s contention that Claims 1-23 of U.S. Patent No. 7,879,828 are rendered obvious by CN ’550, Pawelczyk, and Naggar.

INTRODUCTION

In this *inter partes* review matter, Apotex asserted that a person of ordinary skill in the art ("POSA") would have been motivated to solve the salient problem in the field—tigecycline's chemical instability, particularly due to epimerization—by combining three prior art references to make and use the claimed composition containing tigecycline and lactose in the recited molar ratios and pH ranges. Following the institution decision, Apotex's argument was (1) discredited by the candid admissions of its expert under oath, (2) refuted by Wyeth and its experts, and (3) rejected by the Board on the basis of numerous factual findings that Apotex does not (and, on this record, cannot) challenge under the applicable substantial evidence standard.

Rather than attempt to find error in the Board's rejection of the argument it advanced, Apotex castigates the Board (1) for applying a legal standard that the Board explicitly did not apply and (2) for declining to address motivation arguments that in fact were rejected by the Board and, in any event, are necessarily insufficient to render the claims of the '828 patent obvious in light of the Board's holdings.

With respect to its first argument on appeal, Apotex alleges that the Board "erred by importing an 'epimeric stability' limitation into the claims" and thereby required that the prior art demonstrate epimeric stability. Br. 21, 21-25. But the

Board did no such thing. Precisely to the contrary, it held that "Petitioner [Apotex] is correct that the claims do not recite epimeric stability and therefore obviousness of the claims can be demonstrated without a showing of epimeric stability in the prior art." A14 (Final Decision). The notion that the Board erred by importing an epimeric stability limitation into the claim and requiring that it be demonstrated in the prior art cannot be squared with the Board's explicit rejection of that which Apotex now deems erroneous.

Apotex's second argument asserts legal error on the basis that the "Board erred in failing to consider motivations beyond the [epimeric stability] problem the patentee was trying to solve." Br. 25, 25-30. In particular, Apotex advances three specific arguments it asserts the Board should have considered. Br. 28-30.

Contrary to Apotex's protestations on appeal, the Board's consideration of the motivation issue did not "fail[] to consider motivations beyond" epimeric stability. Br. 25, 25-30. Rather, after expressly declining to limit its motivation analysis to the problem of epimerization, and addressing each of the arguments presented by Apotex, the Board concluded as a matter of fact: "Petitioner, therefore has not provided sufficient rationale to explain why a person having ordinary skill in the art would have substituted tigecycline for minocycline in the CN '550 compositions **for any reason**, much less in an attempt to make a lyophilized tigecycline composition that was stable against epimerization on this

basis, as Petitioner contends." A12 (Final Decision) (emphasis added).

As to the three motivations that Apotex now alleges the Board erred by ignoring, the first was, in fact, considered by the Board and addressed in its Final Decision. The second and third arguments, among other infirmities, only address the pH of the composition, rather than the dispositive question of whether a POSA would have been motivated to combine tigecycline with lactose. Unless Apotex demonstrates that the Board's finding as to the tigecycline and lactose claim limitations was unsupported by substantial evidence—a finding that Apotex does not even attempt to challenge—these subsidiary arguments that a POSA would have used a pH within the claimed ranges necessarily are insufficient to render the claims of the '828 patent obvious.

In short, in addressing the question of motivation, the Board acknowledged, addressed, and rejected every argument Apotex advanced in support of its assertion that the instituted combination of CN '550, Naggar, and Pawelczyk would have provided a reason for the POSA to prepare the claimed compositions. The Board "focus[ed] heavily on the issue of epimerization," Br. 18, for the simple reason that Apotex's motivation arguments focused heavily on epimerization. Apotex now seeks to blame the Board for the consequences of its own strategic decision (compelled by the overwhelming record regarding the problem a POSA would have tried to solve as of the priority date) to argue that the references would have

motivated a POSA to solve the chemical instability problem using lactose and tigecycline at the claimed molar ratios and pH ranges. In deciding that determinative question in Wyeth's favor, the Board made numerous, unchallenged factual findings that mandate affirmance of the judgment below.

STATEMENT OF THE FACTS

Because Apotex's Opening Brief mischaracterized and omitted several aspects of the record below, Wyeth submits this Statement of Facts for completeness. In particular, both of Apotex's arguments are premised on the idea that it was inappropriate for the Board to focus on the stability and epimerization problem. However, as set forth below, it was Apotex itself that introduced, and throughout the proceedings below consistently pursued, epimerization as the primary theory of motivation in its obviousness case. Naturally, Wyeth responded to these arguments, and the Board evaluated them.

I. The '828 Patent

U.S. Patent No. 7,879,828 ("'828 patent") is directed to pharmaceutical compositions of tigecycline that are stable against the two primary forms of chemical degradation that plague tetracycline antibiotics—oxidation and epimerization.

Prior to the filing date of the '828 patent, oxidation was known to be the primary degradation pathway of tetracycline antibiotics—of which tigecycline is

one—at higher pH levels. A220 (Pawelczyk); A1649-50 (Mitscher Decl.); A1799-1800 (Williams Decl.); A1973 at 32:1-6 (Nelson Depo.). At lower pH levels, however, epimerization became the primary degradation pathway. A236 (Ritter at 7:15-19); A1649-50 (Mitscher Decl.); A1799-1800 (Williams Decl.); A1973 at 32:1-6 (Nelson Depo.). Although oxidation and epimerization proceed along different chemical pathways, they both degrade the molecule and, accordingly, reduce the amount of compound available to exert its desired pharmacological effects. A1651-52 (Mitscher Decl.); A1799-1800, 1792-93 (Williams Decl.). Thus, as of the March 14, 2005 priority date, the crucial problem facing a POSA preparing a tigecycline formulation would have been chemical instability due to oxidation and epimerization. A1651-52 (Mitscher Decl.); A1799-1800 (Williams Decl.); A1973 at 32:16-33:10 (Nelson Depo.).

The ’828 patent solved that problem by providing for tigecycline compositions “that achieve stability against both oxidative degradation and epimerization.” A31 (’828 patent at 1:15-18). In particular, the claimed compositions provide for the use of tigecycline and lactose at specified molar ratios and within specified pH ranges. A37-38 (’828 patent).

Claims 1 and 12 are independent claims. Claim 1 covers a composition consisting of tigecycline, lactose, and either hydrochloric or gentisic acid at a molar ratio between about 1:0.2 and about 1:5, and a pH between about 3.0 and

about 7.0. A37 ('828 patent). Claim 12 is identical to claim 1 except that it specifies that the acid used be hydrochloric acid. *Id*. Several of the dependent claims narrow the pH and molar ratio ranges in claims 1 and 12. In particular, the dependent claims cover pH ranges of about 4.0 to about 5.0 (claims 4 and 14), about 4.5 to about 6.0 (claims 10 and 16), about 4.5 to about 5.5 (claims 11 and 17), and about 4.2 to about 4.8 (claims 5 and 15). A37-38 ('828 patent). Other dependent claims narrow the range of the molar ratios of tigecycline to lactose to between about 1:1.6 and about 1:3.3 (claims 9 and 13). *Id*.

II. Proceedings before the Patent Trial and Appeal Board

1. Apotex's Petition

On November 1, 2013, Apotex filed its Petition for *Inter Partes* Review of U.S. Patent No. 7,879,828 ("Petition"), asserting seven grounds of obviousness. A39-106 (Petition). Though the grounds asserted by Apotex differ in their particular combinations of prior art, they all advanced the same motivation to make and use the claimed composition containing tigecycline and lactose in the recited molar ratios and pH ranges: addressing the problem of chemical instability of tigecycline, particularly its epimerization. Along with its Petition, Apotex submitted a declaration from its expert, Dr. Mark L. Nelson. A107-202 (Nelson Decl.). Dr. Nelson's conclusions mirrored the arguments advanced by Apotex and were premised on his opinion that the asserted references taught a solution to the

epimerization of tetracyclines.

Apotex described the invention in the '828 patent as "the discovery that when the pH of a solution containing tigecycline is lowered to reduce oxidative degradation, . . . 'suitable carbohydrates act to stabilize tigecycline against epimer formation at acidic pHs.'" A52 (Petition) (quoting A32 ('828 patent at 4:57-59)). And its theories for the '828 patent's alleged invalidity were based on tigecycline's chemical instability: "An understanding of the chemistry and degradation of tetracycline-class antibiotics, including tetracycline, minocycline and tigecycline, underlies each of the grounds of unpatentability set forth below." A58 (Petition). Every single one of Apotex's seven grounds depended on the argument that the asserted references would have disclosed to a POSA the desirability of using lactose to chemically stabilize a tetracycline other than tigecycline, and that the POSA therefore would have used lactose in the recited molar ratios to prepare a stable composition of tigecycline.[1]

[1] Though this brief focuses on the sole Ground on which the Board instituted trial, each of Apotex's other grounds relied on enhancement of chemical stability as the reason or motivation to use lactose. *See, e.g.*, A70-86 (Ground 1: CN '550 taught that lactose could stabilize tigecycline against epimerization); A90-94 (Ground 3: the Zhang reference teaches a POSA "who is seeking a suitable protonation inhibitor to stabilize a tetracycline against C4 epimerization, as taught by Naggar, to select lactose among the lyophilization stabilizers disclosed in CN '550" (A93)); A94-96 (Ground 4: "Trivedi thus provides further direction for a [POSA] to use lactose as a stabilizer for the lyophilized composition disclosed in CN '550" (A96)); A96-97 (Ground 5: same arguments with respect to combination of Trivedi, CN '550, Naggar, and Pawelczyk); A97-101 (Ground 6: a

Of the seven grounds for unpatentability in Apotex's Petition, the Patent Trial and Appeal Board ("PTAB" or "Board") declined to institute trial on six, finding those grounds "redundant" in light of the ground on which the Board instituted review. A1019 (Institution Decision). Apotex did not seek reconsideration of that decision and does not appeal that decision here. A38.1-38.4 (PTAB Docket); Br. 1 (Statement of the Issues addressing only Ground 2 on which trial was instituted); *Id. passim* (challenging Final Written Decision Ground 2, not the Institution Decision). Ground 2—obviousness over a combination of CN '550, Naggar, and Pawelczyk—was the sole subject of trial before the Board and the appeal to this court. Br. 1, 19-20; A1019-1020 (Institution Decision).

a. Chinese Patent Application No. CN 1390550A ("CN '550")

Apotex's primary reference in Ground 2, and the only reference on which it now relies to provide a reason to use lactose in a tigecycline composition, is Chinese Patent Application No. CN 1390550A ("CN '550"). Apotex's Petition, A39-106, and the accompanying expert declaration of Dr. Mark Nelson, A107-

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POSA "seeking to develop a stable lyophilized formulation of minocycline or tigecycline, using the lyophilization excipients disclosed in CN '550, would be directed by Kirsch and Herman to use lactose in the formulation to reduce degradation of the drug" (A101)); A101-104 (Ground 7: "Lawter discloses an unstable composition of tetracyclines . . . that is ready for stabilization using the prior art stabilizers disclosed in CN '550, and specifically the lactose stabilizer disclosed in Trivedi" (A104)).

202, relied on a translated version of CN '550 to argue (1) that the reference disclosed to a POSA that lactose could be used to prepare chemically stable compositions of minocycline (including compositions stable against epimerization), and (2) that the POSA would then have been motivated by CN '550 and its supposed disclosure of stable minocycline compositions to use lactose to prepare tigecycline compositions with an expectation of successfully addressing the epimerization problem. Apotex's suggestion in its Appeal Brief that its motivation argument to the Board somehow did not involve epimerization is belied by the statements in its Petition.

1. Compositions of minocycline in CN '550. Apotex first tried to argue that a POSA would recognize that CN '550 disclosed a formulation that stabilized minocycline against epimerization. A77 (Petition). The word epimer (or any derivative thereof) does not appear anywhere in CN '550, so Apotex relied on a statement in CN '550 that the claimed formulations had "very good therapeutic effect." A1977 at 46:16-49:23, A1988 at 91:3-93:16 (Nelson Depo.). Dr. Nelson argued that, because the same paragraph included both the disclosure of lactose and the statement that the claimed formulations have "very good therapeutic effect," a POSA would infer that lactose would chemically stabilize minocycline against epimerization (because the epimer is relatively inactive). A1988 at 91:3-93:16, A1983 at 70-71 (Nelson Depo.).

Apotex repeatedly argued that based on those disclosures, a POSA would understand CN '550 to teach that the ingredients disclosed therein—including lactose—were effective to stabilize minocycline against epimerization. A68-69, A77-79 (Petition); A141, A154-55, A159-62 (Nelson Decl.).

2. Substitution of tigecycline for minocycline in the CN '550 compositions. On the premise that CN '550 disclosed that lactose reduced the epimerization of **minocycline**, Apotex argued that a POSA who so interpreted CN '550 would have substituted **tigecycline** for minocycline in the CN '550 formulations. A77-78 (Petition). The reasons Apotex advanced for this second step of its obviousness contention included (1) the known therapeutic efficacy of tigecycline and (2) that minocycline and tigecycline had the same A and B rings and undergo epimerization by the same mechanism and at the same position.[2] A77-78 (Petition); A8-9 (Final Decision). Apotex therefore asserted that a POSA "would understand and expect that lactose would be effective to stabilize minocycline and tigecycline against C4 epimerization" in the formulation taught by CN '550. A78 (Petition).

Apotex did not contend in its Petition that a POSA would have substituted

[2] As explained *infra*, p. 42-47, contrary to its argument before the Board, Apotex now seeks to present its contention regarding the structural similarity of minocycline and tigecycline as somehow distinct from the issue of epimerization. Br. 28.

tigecycline for the minocycline formulations of CN '550 for any reason that was not premised on the assertion that the prior art disclosed that lactose would chemically stabilize minocycline, including against epimerization. A68-69, A77-78 (Petition); A141, A154-55, A159-62 (Nelson Decl.). Apotex repeatedly asserted that preventing epimerization was the motivation for using lactose with tigecycline. For example, Apotex contended:

- "Prior to 2005, it was known that conventional pharmaceutical excipients including monosaccharides such as glucose, disaccharides such as lactose, and polysaccharides such as dextran are effective to stabilize tetracycline antibiotics against degradation by **epimerization**, in lyophilized formulations and in acidic solution, as disclosed, for example, in Ex. 1004, CN '550, trans. 3:32-37 (lactose, glucose, dextran and mannitol)." A68-69 (Petition) (emphasis added);

- "CN '550 discloses a composition of minocycline, a lyoprotectant, and a pH adjusting agent, having a pH in a solution of 2.0 to 3.5, that is stable against degradation, which necessarily includes degradation by **epimerization** in an aqueous solution at an acid pH." A77 (Petition) (emphasis added);

- "Both minocycline and tigecycline undergo C4 epimerization at a pH of 2.0 to 3.5. A person of ordinary skill in the art would understand and expect that lactose would be effective to stabilize minocycline and tigecycline against C4 **epimerization** in a solution having a pH from 0.1-7.5, including an acid pH of 2.0-3.5, as taught by CN '550, based on the exact structural identify of the A and B rings in these analogs." A78 (Petition) (internal cites removed) (emphasis added);

- "A person of ordinary skill in the art would expect each of the saccharide excipients disclosed in CN '550 to be effective to stabilize minocycline and tigecycline against C4 **epimerization** in a solution having a pH from 0.1-7.5, including an acid pH of 2.0-3.5, because of the structural similarities of glucose (a monosaccharide), lactose (a disaccharide), and dextran (a polysaccharide)." A78 (Petition)

(emphasis added);

- "A person of ordinary skill in the art in 2005, seeking to stabilize a lyophilized tigecycline composition, including a composition having a pH in a solution from 0.1 to 7.5, or a pH from 2.0 to 3.5, would be motivated by CN '550 to select lactose, which is one of the most commonly-used pharmaceutical excipients, to stabilize the lyophilized composition against **epimerization**." A79 (Petition) (emphasis added);

- "A person of ordinary skill in the art would understand and expect that lactose would be effective to stabilize minocycline and tigecycline against C4 **epimerization** in a solution having a pH from 0.1-7.5, including an acid pH of 2.0-3.5, as taught by CN '550, based on the exact structural identity of the A and B rings in these analogs." A78 (Petition) (emphasis added), citing A161-162 (Nelson Declaration); A13 (Final Decision).

Accordingly, even Apotex's arguments for using lactose with tigecycline that relied on the properties of tigecycline—such as its alleged chemical similarity to minocycline in the A and B rings where epimerization occurs—were premised explicitly on the assertion that a "person of ordinary skill in the art would understand and expect that lactose would be effective to stabilize minocycline and tigecycline against C4 epimerization." A78 (Petition).

Along with its Petition, Apotex submitted a declaration from its expert, Dr. Mark L. Nelson. A107-202. Not surprisingly, this declaration, too, focused almost exclusively on epimeric stability as the motivation guiding the POSA to arrive at the claimed invention. Apotex relied on Dr. Nelson's assertions that:

- "CN '550 discloses that the lyophilized powder is stabilized under acidic conditions, and a [POSA] would readily appreciate that

stabilization would include prevention of C4 **epimerization** in an acidic solution by the disclosed excipients." A154-55 (Nelson Decl.) (emphasis added);

- CN '550 discloses "a composition of minocycline, an excipient, and a pH adjusting agent, having a pH in a solution of 2.0 to 3.5, that is stable against degradation, which necessarily includes degradation by **epimerization** at an acid pH." A159-60 (Nelson Decl.) (emphasis added);

- "CN '550 discloses that lactose, glucose, dextran and mannitol can inhibit epimerization in a lyophilized powder when minocycline is formulated as the HCl salt and added to excess carbohydrate in a solution having a pH from 0.1 to 7.5, or 2.0 to 3.5, which are conditions under which C4 **epimerization** occurs." A141 (Nelson Decl.) (emphasis added);

- "A person of ordinary skill in the art would expect each of the saccharide excipients disclosed in CN '550 to be effective to stabilize minocycline and tigecycline against C4 **epimerization** in a solution having a pH from 0.1-7.5, including an acid pH of 2.0-3.5, because of the structural similarities of glucose (a monosaccharide), lactose (a disaccharide), and dextran (a polysaccharide)." A161 (Nelson Decl.) (emphasis added);

- "For the reasons stated above in more detail . . . , it was known in the prior art, including CN '550, that suitable carbohydrates including disaccharides such as lactose, monosaccharides such as glucose, and polysaccharides such as dextran, are effective to stabilize tetracyclines against **epimerization** at acid pHs." A161 (Nelson Decl.) (emphasis added);

- "A person of ordinary skill in the art would understand and expect that lactose would be effective to stabilize minocycline and tigecycline against C4 **epimerization** in an a [sic] solution having a pH from 0.1-7.5, including an acid pH of 2.0-3.5, as taught by CN '550, based on the exact structural identity of the A and B rings in these analogs." A161-162 (Nelson Decl.) (emphasis added);

- "A person of ordinary skill in the art in 2005 seeking to stabilize a lyophilized tigecycline composition, including a composition having a

> pH in a solution from 0.1 to 7.5, or a pH from 2.0 to 3.5, would thus be motivated by CN '550 to select lactose, which is one of the most commonly-used pharmaceutical excipients, to stabilize the lyophilized composition against **epimerization**." A162 (Nelson Decl.) (emphasis added).

Like Apotex's Petition, Dr. Nelson's motivation arguments, including the contention regarding "structural identity of the A and B rings" in minocycline and tigecycline, all were premised on the allegation that the prior art taught that "lactose would be effective to stabilize . . . against C4 epimerization." A161-62 (Nelson Decl.). Dr. Nelson focused on epimerization because he recognized that chemical instability was the problem that a POSA would have addressed. He readily agreed that "when a [POSA] is confronting a new tetracycline and trying to prepare a composition, that person would know that the problems they face are oxidation and epimerization." A1973 at 32:16-33:10 (Nelson Depo.).

b. V. Naggar et al., *Effect of Solubilizers on the Stability of Tetracycline*, Pharmazie 29(2) 126-129 (1974) ("Naggar")

Apotex also relied on Naggar to contend that a POSA would have believed that lactose could stabilize tetracyclines against epimerization at the claimed pH ranges. Naggar discloses neither tigecycline nor lactose, but unlike CN '550, it expressly addresses epimerization. Naggar discloses the use of certain "solubilizers" to reduce epimerization of tetracycline[3] (not tigecycline, which had

[3] Tetracycline is a compound within the tetracycline class.

not yet been synthesized at the time of the Naggar article). A224-25 (Naggar). In particular, it discloses that thiourea, PEG 6000, and, to a lesser extent, urea and polysorbate 20, slightly reduced the rate of epimerization of tetracycline. *Id*. Naggar also discloses that epimerization of tetracycline occurs at pH 2-6, and takes place most rapidly in the pH range of 3-4. *Id*; A8 (Final Decision).

In its Petition, Apotex argued that the use of the solubilizer polysorbate 20 in Naggar would have motivated a POSA to use saccharides—like lactose—to stabilize tigecycline against epimerization, A89-90 (Petition); A172-73 (Nelson Decl.), notwithstanding the absence of evidence that lactose is a solubilizer. A1584-85 (Patent Owner Response); A1638-40, A1699-1702 (Mitscher Decl.); A1784-85, A1832-35 (Williams Decl.). Apotex's argument below, on which the Board instituted review, was that "Naggar teaches that tetracyclines are stabilized against epimerization by hydrogen bonding between a saccharide (such as lactose) and a tetracycline." A1017 (Institution Decision).

Apotex argued that the combination of Naggar and CN '550 rendered it obvious to use an acidic solution with lactose to stabilize tigecycline against epimerization. A89 (Petition). Dr. Nelson even attempted to articulate a theory about the chemical mechanism by which epimerization could be reduced using the ingredients disclosed in CN '550 and Naggar. A89-90 (Petition).

Both Apotex's argument with respect to Naggar and Dr. Nelson's proposed

chemical mechanism were thoroughly discredited by trial, such that Apotex essentially abandoned this central motivation theory of its Petition, both before the Board and this Court. A86-90 (Petition); A7117-7119, A7119 (Apotex's Reply) ("[t]he Board does not need to resolve the dispute concerning the mechanism of stabilization by which lactose and other saccharides inhibit epimerization"); A10219-91 (Hearing Tr.); Br. 1-31.

c. E. Pawelczyk et al., *Kinetics of Drug Decomposition. Part 74. Kinetics of Degradation of Minocycline in Aqueous Solution*, Pol. J. Pharmacol. Pharma. 34:409-421 (1982) ("Pawelczyk")

Apotex relied on Pawelczyk solely for its disclosure regarding pH. There is no disclosure in Pawelczyk of either tigecycline or lactose, nor is there any discussion of epimerization. A216-23 (Pawelczyk); A1642 (Mitscher Decl.); A1785-86 (Williams Decl.). With respect to pH, Pawelczyk teaches that oxidation is the primary degradation pathway of minocycline at pH above 5.0, and proposes potential solutions to that problem. *See* A216-23 at A220 (Pawelczyk); A8 (Final Decision). Thus, Apotex argued that the claimed pH ranges would have been obvious for chemically stabilizing tigecycline. *See, e.g.*, A87 (Petition) ("Pawelczyk expressly teaches that oxidation of a solution containing a tetracycline such as minocycline is reduced if the pH is reduced to below 5.0, and discloses aqueous solutions of pH 4.2 and 5.2 . . . as well as pH 4.38, 4.86, and 5.42."); A87-89 (Petition); A170 (Nelson Decl.) ("Pawelczyk concludes that

'oxidation is a predominant process of [minocycline] degradation above pH 5.' . . . Pawelczyk thus clearly teaches that a pH range below 5 is preferable to avoid oxidative degradation of minocycline 'in a solution.'"); A170-72 (Nelson Decl.). Neither Apotex nor its expert Dr. Nelson asserted that disclosures of pH in Pawelczyk or elsewhere somehow would have motivated a POSA to use lactose. A87-89 (Petition); A170-72 (Nelson Decl.).

2. Wyeth's Response

a. CN '550

Wyeth and its experts provided numerous reasons that the asserted prior art would not have motivated a POSA to prepare a tigecycline composition with lactose in the claimed molar ratios and pH ranges.

Wyeth presented at least six distinct arguments to refute Apotex's contention that CN '550—the only reference that mentioned lactose—would have motivated a POSA to use it with tigecycline.

First, Wyeth explained that CN '550 contains no disclosure whatsoever relating to epimerization; the word "epimer" never appears in the reference, nor is there any data relating to epimerization. A1677-81 (Mitscher Decl.); A1816-17 (Williams Decl.). Moreover, the statement in CN '550 that the invention "features stable light, thermal, oxygen, and water properties" would not have indicated to the POSA that the claimed compositions were stable against epimerization, which is a

separate category of stability that would have been addressed expressly if relevant. *See* A1678-79 (Mitscher Decl.); A1816-18 (Williams Decl.); A1816 (Williams Decl.) ("A [person of ordinary skill in the art] simply would not believe that a reference solves an epimerization problem if it neither mentions epimerization, nor provides any analytical data relating to epimerization."). Prior art references that addressed the epimerization problem said so, as demonstrated by numerous examples in the prior art. A1754-1758 (Mitscher Decl.) (discussing prior solutions to the epimerization of tetracyclines found in the literature that explicitly address epimerization of tetracyclines, including A654-63 (Moreno-Cerezo), A232-37 (U.S. Patent No. 5,122,519), and A2665-80 (U.S. Patent No. 4,701,320)).

Second, Wyeth argued that the statement that the invention has "very good therapeutic effect" does not indicate that the formulation was stable against epimerization because the tests used to evaluate a compound's activity shed no light on the stability of a formulation containing that compound. A1654, A1687-90 (Mitscher Decl.); A1796-98, A1818, A1821-22 (Williams Decl.).

Third, the POSA would understand the term used in CN '550 to describe lactose and the other ingredients—"lyophilized powder supporting agent"—to be a "specific term of art referring to an ingredient that provides **physical** support to a lyophilized powder formulation, so that it continues to occupy the same space, rather than collapsing." A1576 (Patent Owner Response) (emphasis added);

A1576-80 (Patent Owner Response). In other words, the POSA would understand that the invention claimed in CN '550 related only to **physical** stability of the lyophilized powder, not **chemical** stability (such as epimeric stability) of the active ingredient contained therein. A1682-83 (Mitscher Decl.); A1814-15 (Williams Decl.). Dr. Nelson agreed that protecting molecules from degradation by deprotonation (and thus epimerization) is a function of some types of excipients, but not lyophilized powder supporting agents. A1997 at 126:14-127:24 (Nelson Depo.).

Fourth, the six lyophilized powder supporting agents identified in CN '550—ranging from sodium chloride (table salt) to hydrolyzed gelatin—vary widely in their chemical structures and properties, such that a POSA would not expect them to participate in the same or similar chemical interactions with minocycline, as required to prevent epimerization. A1690-92 (Mitscher Decl.). As Wyeth's expert explained, a POSA "would have concluded that [both sodium chloride and lactose are] acting as lyophilized powder supporting agents that provide physical support to the formulation, rather than interacting with the minocycline by forming a hydrogen bond" and thereby stabilizing it against epimerization. A1692 (Mitscher Decl.).

Fifth, the specification and claims of CN '550 do not require that any lyophilized powder supporting agent be used at all; rather, they disclose a

composition with "0-100 parts lyophilized powder supporting agent." A1394-97 (CN '550). Wyeth's experts explained that "if the soluble support were necessary to chemically stabilize the drug, its inclusion in the formulation would be required." A1694 (Mitscher Decl.); A1821 (Williams Decl.).

Sixth, Wyeth's expert chemist noted that the three exemplified formulations in CN '550 (none of which contains lactose) disclosed particular **weight** ratios of lyophilized powder supporting agent to minocycline, rather than **molar** ratios. Because a chemical interaction—such as stabilizing against epimerization—would occur in a particular molar ratio, the disclosure of weight ratios would suggest to the POSA that the listed ingredients were only interacting physically with the minocycline to support the lyophilized cake. A1735 (Mitscher Decl.).

b. Naggar

With respect to Naggar, Wyeth pointed out that even Apotex's own expert disavowed the motivation argument presented in Apotex's Petition and adopted preliminarily by the Board. When asked about the statement (from the Board's Institution Decision at A1017) that "Naggar teaches that tetracyclines are stabilized against epimerization by hydrogen bonding between a saccharide (such as lactose) and a tetracycline," Dr. Nelson candidly admitted that "[Naggar] says nothing about that." A2026 at 245:7-12 (Nelson Depo.); A1587-88 (Patent Owner Response).

Wyeth and its experts demonstrated that Naggar does not disclose that saccharides such as lactose are effective at stabilizing tetracyclines; rather, it discloses that "solubilizers" may stabilize tetracyclines to a minor extent, but lactose is not a solubilizer. A1584-85 (Patent Owner Response); A1638-40, A1699-1702 (Mitscher Decl.); A1784-85, A1832-35 (Williams Decl.).

c. Pawelczyk

Wyeth's experts also demonstrated that Pawelczyk, which addresses minocycline, taught that tigecycline should not be formulated above a pH of 3.6, in order to successfully control oxidative degradation using pH. *See* A1600-02 (Patent Owner Response); A1728-32 (Mitscher Decl.). Apotex's expert, Dr. Nelson, agreed that on the basis of Pawelczyk, a POSA would not have wanted to prepare a composition containing tigecycline at a pH above 4.4, A2042 at 307:2-16 (Nelson Depo.), which is outside the pH ranges of claims 10, 11, 16, 17, 22, and 23 of the '828 patent.

3. Apotex's Reply

Apotex chose not to submit an expert declaration to respond to the foregoing evidence, including the admissions of its own expert. Apotex's Reply for the first time cited the legal theory that a motivation other than chemical stability could be relevant, but did not provide any reason to use lactose and then substitute tigecycline for minocycline other than to reduce epimerization. *See* A7114-17

(Apotex's Reply).

4. The Board's Final Written Decision

After weighing the evidence before it, the Board issued a Final Written Decision, finding that Apotex had not shown that a POSA would have had reason to make the compositions recited in the challenged claims. A9-22 (Final Decision).

On the basis of Wyeth's arguments, the Board considered and conclusively rejected Apotex's interpretation of CN '550, its lead obviousness reference. A9-22 (Final Decision). The Board explicitly found that "a person having ordinary skill in the art would not have looked to a reference," such as CN '550, "that does not mention epimerization," A18, that "there are no statements from which a person skilled in the art would understand that the CN '550 formulations were epimerically stable," A15, and that Apotex's interpretation of the language in CN '550 was unsupported by "any objective evidence or analysis," A16. Apotex does not challenge these findings as unsupported by substantial evidence on appeal. Br. 1-3, 19-30.

The Board found that Apotex and Dr. Nelson's focus on "Naggar's disclosure of polysorbate 20 over other solubilizers disclosed therein (when Naggar indicates that other solubilizers worked better)" was the product of hindsight. A21-22 (Final Decision). Moreover, Apotex could not persuade the

Board that a POSA in view of Naggar "would have used lactose instead of polysorbate 20 in any event, when the reference does not mention other polysaccharides, much less lactose in particular." A21 (Final Decision).

Taken together, on the basis of the entire record, the Board deemed "unpersuasive" Apotex's evidence that a POSA would have combined the elements of the claims from the prior art, holding that "Petitioner attempts to imbue one of ordinary skill in the art with knowledge of the claimed invention, when no prior art reference or references of record conveys or suggests that knowledge." A22 (Final Decision). The Board concluded that "Petitioner's argument that CN '550 is combinable with Pawelczyk and Naggar appears to be premised on Petitioner's knowledge of the '828 patent's disclosure of lyophilized compositions of tigecycline and lactose that are stable against epimerization." A22 (Final Decision).

Furthermore, the Board held that Apotex had not established that a POSA would have had reason to believe that tigecycline would have been stabilized by the formulations disclosed in CN '550. A14 (Final Decision). The Board agreed with Apotex that the claims of the '828 patent do not recite epimeric stability and that obviousness can be demonstrated without a showing of epimeric stability in the prior art, but held that "[w]e are not persuaded, however, that Petitioner has established that a person having ordinary skill in the art would have found it

obvious to substitute tigecycline for minocycline in the composition disclosed in CN '550." A14 (Final Decision). Apotex does not challenge these factual findings as unsupported by substantial evidence.

The Board's decision also recognized Apotex's assertion that if a POSA had interpreted CN '550 to disclose stabilized compositions containing **minocycline**, then the properties of tigecycline—including its antibacterial potency and its alleged structural similarity in the A and B rings where epimerization occurs—would have motivated a POSA to substitute tigecycline in place of minocycline. A12-13 (Final Decision). Consistent with the record, including the arguments advanced by Apotex's Petition, the Board rejected the arguments, which "presume that a person of ordinary skill in the art would have recognized that the compositions disclosed in CN '550 were stable against epimerization." A13. The Board disagreed with that premise and, more generally, rejected the contention that a POSA "would have substituted tigecycline for minocycline in the CN '550 compositions for any reason"—another determinative factual finding that Apotex does not challenge on appeal. A12.

SUMMARY OF THE ARGUMENT

Apotex's brief reads as if trial in this matter had never occurred, and the Board did not reject resoundingly its Petition's basis for using lactose in the claimed tigecycline compositions. Apotex attempts to erase the statements in its

Petition, the admissions of its expert, the credited testimony of Wyeth's expert, and the Board's numerous and unchallenged factual findings—including its conclusion that a POSA would not have used lactose with tigecycline for any reason.

In place of this inconvenient record, Apotex crafts a different narrative, asserting two alleged errors that bear no relationship whatsoever to the facts presented here. Apotex first contends that the Board committed error "by importing an 'epimeric stability' limitation" into the '828 patent claims and applying a legal standard that required a showing of epimeric stability in the prior art. Br. 21, 21-25. In reality, however, the Board did precisely the opposite. The Board explicitly agreed with Apotex, holding that "Petitioner is correct that the claims do not recite epimeric stability and therefore obviousness of the claims can be demonstrated without a showing of epimeric stability in the prior art." A14 (Final Decision).

Because Apotex's Petition and accompanying evidence relied on reducing epimerization to fulfill the requirement that the challenger provide a reason to make or use the claimed invention, the Board addressed that argument and ultimately rejected it. It is not error to consider the arguments that Apotex advanced below, and the Board clearly did not require that Apotex's motivation arguments be based on epimerization.

Apotex's second argument—that the Board erred by "failing to consider

motivations beyond the problem the patentee was trying to solve (minimizing epimerization)," Br. 20—is likewise unavailing. Again, Apotex's position is based on a fundamental misreading of the Board's decision. The Board found the POSA would not have made the claimed compositions "for any reason," not just to address epimerization. A12 (Final Decision). Nonetheless, Apotex proceeds here as if it had filed a different Petition, identifying three motivation arguments that the Board supposedly failed to address. Br. 28-29. The first—that the alleged "structural similarity" of minocycline and tigecycline, "including the identity of their A and B rings" where they undergo epimerization, would have motivated substitution of tigecycline for minocycline, Br. 28—was not ignored by the Board; it was expressly recognized, documented in the Board's Final Decision, and rejected. A8-9, A13 (Final Decision). That factual determination was supported by substantial evidence.

Apotex's second and third supposed motivation arguments relate to the pH ranges disclosed, respectively, in the asserted Pawelczyk and Naggar references and in various other references that were not at issue at trial. Br. 29. These pH motivation theories necessarily fail, as they do not address the outcome-determinative question of whether a POSA would have had reason to use lactose in a tigecycline composition—they relate only to the pH a POSA would seek to use. Apotex's inability to prove the obviousness of making a tigecycline composition

with lactose simply cannot be overcome by an argument that, if the POSA had wanted to make the composition, the claimed pH ranges would have been used.

This appeal presents nothing more than an aggrieved litigant facing a factual rejection of its interpretation of the prior art and its motivation theory. Because those factual findings are fatal to Apotex's case and are supported by substantial evidence, Apotex seeks to conjure a contention of legal error by mischaracterizing its own arguments and the Board's decision rejecting them. The Court should reject Apotex's arguments and affirm the Board's decision.

STANDARD OF REVIEW

This Court reviews the Board's ultimate determination of obviousness *de novo*, and the factual findings underlying that determination for substantial evidence. *In re Urbanski*, ---F.3d.---, 2016 U.S. App. Lexis 215, *7 (Fed. Cir. Jan. 8, 2016). *See also In re Baxter Int'l, Inc.*, 678 F.3d 1357, 1361 (Fed. Cir. 2012). "A finding is supported by substantial evidence if a reasonable mind might accept the evidence to support the finding." *Id.*; *see also In re Kotzab*, 217 F.3d 1365, 1369 (Fed. Cir. 2000).

The obviousness inquiry asks whether "the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art." 35 U.S.C. § 103(a) (pre-AIA); *accord KSR Int'l*

Co. v. *Teleflex, Inc.*, 550 U.S. 398, 405 (2007). The ultimate determination of obviousness under 35 U.S.C. § 103 is a question of law based on underlying factual findings. *In re Baxter*, 678 F.3d at 1361 (citing *Graham* v. *John Deere Co.*, 383 U.S. 1, 17-18 (1966)).

The determinations of what a reference teaches and the differences between the claimed invention and the prior art are questions of fact that the Court reviews for substantial evidence. *In re Baxter*, 678 F.3d at 1361. The meaning of a prior art reference to a POSA is a question of fact, as is the question of whether a POSA would have had a reason or motivation to make and use the claimed invention. *In re Urbanski*, ---F.3d---, 2016 U.S. App. Lexis 215, at *7 ("Obviousness is a question of law based on underlying factual findings, *In re Baxter*, 678 F.3d 1357, 1361 (Fed. Cir. 2012), including what a reference teaches, *In re Beattie*, 974 F.2d 1309, 1311 (Fed. Cir. 1992), the existence of a reason to combine references, *In re Hyon*, 679 F.3d 1363, 1365-66 (Fed. Cir. 2012), and whether the prior art teaches away from the claimed invention, *In re Mouttet*, 686 F.3d 1322, 1330 (Fed. Cir. 2012).").

ARGUMENT

I. The Board Expressly Did Not Import an Epimeric Stability Limitation Into the Claims.

Apotex's first argument on appeal is that the Board improperly imported an epimeric stability limitation into the claims, in violation of *Senju Pharmaceutical*

Co. v. *Lupin Ltd.*, 780 F.3d 1337 (Fed. Cir. 2015). Br. 21-25. This argument fails for the simple reason that—at Apotex's urging below—the Board did not import any such limitation. Rather, the Board agreed with Apotex, and applied the precise standard Apotex urges here. A12, A14 (Final Decision).

Specifically, in its Reply Brief before the Board, Apotex argued that "the '828 patent claims do not relate to a method for stabilizing tigecycline against epimerization . . . or indeed, to any method of stabilizing tigecycline." A7095. Apotex proceeded to argue on that basis, as it does on appeal, that "[t]he issue is whether a POSA would have found it obvious to make the claimed composition, by substituting tigecycline for minocycline in the composition disclosed in CN '550, for ***any*** reason, not just to reduce epimerization." *Id.* (citations omitted) (emphasis in original).

In its Final Written Decision, the Board acknowledged this argument and agreed with Apotex, stating: "Petitioner is correct that the claims do not recite epimeric stability and therefore obviousness of the claims can be demonstrated without a showing of epimeric stability in the prior art." A14. In other words, the Board adopted the exact legal standard Apotex advocates. Applying Apotex's standard, the Board concluded: "Petitioner, therefore, has not provided sufficient rationale to explain why a person having ordinary skill in the art would have substituted tigecycline for minocycline in the CN '550 compositions for any

reason, much less in an attempt to make a lyophilized tigecycline composition that was stable against epimerization on this basis, as Petitioner contends." A12 (Final Decision).

Unable to argue reversal of this determinative finding under a substantial evidence standard, Apotex now asserts that the Board erred in applying the very legal standard that Apotex itself urged. This argument cannot succeed, except perhaps in providing an exemplary definition of the word *chutzpah*.

To be sure, the Board considered epimeric stability, but not as a claim limitation that had to be demonstrated in the prior art. Rather, the Board considered epimerization in precisely the same manner as presented in Apotex's Petition: as an important problem that the POSA preparing a composition of tigecycline would have wanted to address. The Board's decision is indeed "replete with references to epimerization and epimeric stability," Br. 24, as Apotex notes, but far less so than Apotex's Petition and accompanying expert declaration. A39-106 (Petition); A107-202 (Nelson Decl.). In fact, the Petition used a version of the word "epimerization" 91 times.

For this reason, it is remarkable that Apotex claims that the Board "unduly focused on this concept." Br. 24. Apotex's principal motivation argument for using lactose, on which all of its subsidiary arguments were premised, was that a POSA would have wanted to make the claimed invention to address the problem of

chemical instability, including epimerization. *See supra* p. 9-15; A68-69, A77-79, A87-90 (Petition); A141, A154, A161-62, A170-73 (Nelson Decl.). To the extent there was "undue" focus on epimerization before the Board, it was because Apotex chose to present, and the Board therefore adjudicated, a theory of motivation to address epimerization. Apotex cannot escape the consequences of that decision by deeming erroneous the Board's decision to apply the very claim construction and legal standard that Apotex advanced.

II. The Board Did Not Improperly Limit Its Motivation Analysis and Considered All the Motivations Asserted by Apotex Below.

Apotex's second argument on appeal is that the Board improperly limited its consideration only to the particular problem the patentee was trying to solve—stabilizing tigecycline compositions against epimerization—and that as a result, the Board failed to consider three specific motivation arguments. Br. 25, 25-30.

Apotex cannot manufacture a legal dispute with this allegation. Apotex relies on *KSR* for the proposition that "neither the particular motivation nor the avowed purpose of the patentee controls," and instead argues that "'***any*** need or problem' in the field at the time of invention and addressed by the patent can provide a reason to combine prior art elements." Br. 26 (emphasis in original) (citing *KSR*, 550 U.S. at 419-20); Br. 27 (quoting *Alcon Research, Ltd.* v. *Apotex Inc.*, 687 F.3d 1362, 1368-69 (Fed. Cir. 2012)). Wyeth does not disagree, and the Board explicitly cited and applied that principle. A14 (Final Decision) (citing

A7114 (Apotex's Reply)).

Specifically, the Board agreed with Apotex that "obviousness of the claims can be demonstrated without a showing of epimeric stability in the prior art," but required some reason to combine the references and to make the claimed invention. A14 (Final Decision) (citing A7114 (Apotex's Reply)). Indeed, it was undisputed, both before the Board and here, that the law requires a challenger to establish **some** actual reason or motivation in the field to combine the prior art references to make the claimed invention. *See KSR*, 550 U.S. at 421 (proper analysis asks whether there was "a design need or market pressure to solve" a problem); *Eisai Co.* v. *Dr. Reddy's Labs., Ltd.*, 533 F.3d 1353, 1359 (Fed. Cir. 2008) (the *KSR* inquiry "assumes a starting reference point or points in the art, prior to the time of invention, from which a skilled artisan might identify a problem and pursue potential solutions"); *InTouch Techs., Inc.* v. *VGo Communs., Inc.*, 751 F.3d 1327, 1347 (Fed. Cir. 2014) (a court must "determine whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue") (quoting *KSR*, 550 U.S. at 418); *Procter & Gamble Co.* v. *Teva Pharms. USA, Inc.*, 566 F.3d 989, 994 (Fed. Cir. 2009) (a patent challenger must "demonstrate 'by clear and convincing evidence that a skilled artisan would have been motivated to combine the teachings of the prior art references to achieve the claimed invention'") (quoting *Pfizer, Inc.* v. *Apotex, Inc.*, 480 F.3d 1348, 1361

(Fed. Cir. 2007)); *Institut Pasteur* v. *Focarino*, 738 F.3d 1337, 1346 (Fed. Cir. 2013); Br. 28-29.

Applying this standard, the Board considered and rejected all of the motivation arguments Apotex advanced to combine the asserted prior art references in order to use lactose with tigecycline. A9-22 (Final Decision). That the Board focused on and rejected Apotex's epimerization-based motivation argument does not mean the Board committed error, and the specific motivations Apotex offers here do not rescue Apotex's failed efforts below.

1. The Board Did Not Commit Legal Error by Focusing on Epimeric Stability, Given Apotex's Own Focus on Epimeric Stability as the Motivation.

Apotex focused on epimeric stability at every stage of the IPR proceeding below, and cannot now fault the Board for considering that very argument.[4]

a. Apotex's Petition Focused on Epimeric Stability.

Apotex's Petition to the Board focused almost exclusively on the issue of epimeric stability. After characterizing the invention of the '828 patent as the discovery that "suitable carbohydrates act to stabilize tigecycline against epimer formation at acidic pHs," A52, Apotex devoted thirteen pages of its Petition to

[4] Apotex's attempts to fault Wyeth's expert Dr. Mitscher for limiting his opinions to epimerization fail for the same reason. *See* Br. 25 n.7, 27-28 n.8. As a responsive expert, Dr. Mitscher responded to the arguments set forth by Apotex in the Petition and Dr. Nelson's accompanying Declaration, which were focused almost exclusively on the question of whether the POSA would have combined tigecycline and lactose in an attempt to stabilize tigecycline against epimerization.

background information on the "Chemistry and Degradation of Tetracycline Antibiotics," A58-70 because, Apotex emphasized, it "underlies each of the [asserted] grounds of unpatentability." A58. Most relevantly, with respect to Ground 2—the only ground on which the Board instituted review, A1019 (Institution Decision)—Apotex contended that the asserted references disclosed that lactose could stabilize minocycline compositions against epimerization and that a POSA "would understand and expect that lactose disclosed in CN '550 **would also be effective to stabilize tigecycline against epimerization** in solutions having a pH in the range from 4 to 6 taught as optimal by Naggar." A90 (emphasis added).

A review of the complete record, as opposed to the misleading snippets Apotex cites without context, Br. 25-30, leads to the ineluctable conclusion that the motivation argument raised by Apotex focused on epimerization. *See supra* p. 9-15; A68-69 (Petition) ("Prior to 2005, it was known that conventional pharmaceutical excipients including monosaccharides such as glucose, disaccharides such as lactose, and polysaccharides such as dextran are **effective to stabilize tetracycline antibiotics against degradation by epimerization**, in lyophilized formulations and in acidic solution, as disclosed, for example, in Ex. 1004, CN '550, trans. 3:32-37 (lactose, glucose, dextran and mannitol).") (emphasis added), A78 (Petition) ("A person of ordinary skill in the art would

expect each of the saccharide excipients disclosed in CN '550 to be **effective to stabilize minocycline and tigecycline against C4 epimerization** in a solution having a pH from 0.1-7.5, including an acid pH of 2.0-3.5, because of the structural similarities of glucose (a monosaccharide), lactose (a disaccharide), and dextran (a polysaccharide).") (emphasis added). Apotex cannot simply wish away that record.

b. Apotex's Expert Focused on Epimeric Stability.

Along with its Petition, Apotex submitted a declaration from its expert, Dr. Mark L. Nelson. A107-202. Not surprisingly, this declaration, too, focused almost exclusively on epimeric stability as the motivation guiding the POSA to arrive at the claimed invention. *See supra* p. 13-15; A141, A154-55, 159-62 (Nelson Decl.).

Dr. Nelson focused on epimerization because he recognized that chemical instability was the problem that a POSA would have addressed. He readily agreed that "when a [POSA] is confronting a new tetracycline and trying to prepare a composition, that person would know that the problems they face are oxidation and epimerization." A1973 at 32:16-33:10 (Nelson Depo.). In this respect, both the parties and their respective experts were in full agreement: chemical instability, including epimerization, was the problem that would have motivated a POSA. *Id.*; A1649-51 (Mitscher Decl.); A1651 (Mitscher Decl.) ("Oxidation and

epimerization were well known to be the two primary pathways of degradation for tetracyclines, and a person of ordinary skill in the art formulating a new compound in the class, such as tigecycline, would have focused on these two pathways."); A1798-1800 (Williams Decl.); A1799 (Williams Decl.) ("Dr. Nelson and I are in agreement that a POOS would have considered the main formulation problems to be preparing a composition that is stable to oxidation and epimerization."); A58-64 (Petition); A59-60 (Petition) ("[I]t has long been known that tetracyclines including minocycline and tigecycline undergo oxidative degradation in aqueous solution at a pH that is higher than the pKa of the phenolic group in in [sic] ring D of the tetracycline structure."); A62 (Petition) ("It has also long been known that tetracycline undergoes a reversible epimerization at the dimethylamino group at C4 in the A ring in aqueous solution at a pH between 2 and 6."); A1562-64 (Patent Owner Response); A1563 (Patent Owner Response) ("It was well recognized, and is not disputed by the experts in this case, that the crucial problem facing a POOS preparing a tigecycline formulation would have been instability due to oxidation and epimerization.").

c. In its Reply, Apotex for the First Time Suggested that the Board Look Beyond Epimeric Stability, but Did Not Articulate an Alternate Motivation.

In its Reply Brief, Apotex argued for the first time that the Board need not limit its analysis to epimeric stability, but instead could find the '828 patent

obvious if the POSA would have substituted tigecycline for minocycline in the CN '550 compositions for "any reason." A7114. Yet, Apotex never in fact asserted a reason for using lactose with tigecycline other than to reduce epimerization. Despite paying lip service to a new, broader argument, the heading of the very first subsection under Apotex's argument that "any reason" for substituting tigecycline for minocycline in CN '550 would be sufficient reads, "CN '550 discloses stabilization of tetracyclines against epimerization in acidic solutions." A7116 (Apotex's Reply). Simply put, Apotex could not identify any motivation other than chemical stability to use lactose with tigecycline. Indeed, far from its present plea to shift the focus away from epimerization, Apotex's Reply used the word "epimer," or any derivative thereof, 25 times in only 15 pages of text. In any event, the Board's rules prohibit the presentation of new arguments in the reply brief, and the Board is not obliged to consider them. 37 C.F.R. § 42.23 (b); *Redline Detection, LLC* v. *Star Envirotech, Inc.*, ---F.3d.---, 2015 U.S. App. LEXIS 22897, *25 n.6 (Fed. Cir. Dec. 31, 2015) (In its reply, "a petitioner 'may only respond to arguments raised in the corresponding opposition.' Any new issues raised in the reply will not be considered.") (citing Final Rule, 77 Fed. Reg. at 48,768 and 37 C.F.R. § 42.23).

d. At the Hearing, Apotex Continued to Focus on Epimeric Stability.

Even at the oral hearing, Apotex continued to emphasize the prior art

teachings related to epimeric stability that it argued rendered the claimed invention obvious. Indeed, much like the Board's decision, Apotex's argument at trial was "replete" with references to epimerization, degradation, and stability. *See* A10221-49; 10286-90 (45 references to "epimer" or any derivative thereof).[5]

Lest any doubt remain on the basis of its written submissions, the Board asked Apotex at the hearing to clarify whether its Petition had asserted any motivation other than epimerization for the POSA to combine the elements of the prior art to make the claimed invention. *See* A10287-88 (Hearing Tr.). In response, Apotex pointed only to page 40 of the Petition as offering another argument, namely that CN '550 "would anticipate the claims, if you substituted tigecycline for minocycline." A10288 (Hearing Tr.). Needless to say, that is not a motivation argument. For all its avowed displeasure with the Board's focus on epimerization, Apotex did not present any other actual reason in the field that the POSA would have been motivated to use lactose with tigecycline.

[5] At the hearing, Apotex perfunctorily attempted to suggest that the POSA would have been motivated to use lactose as a bulking agent in tigecycline formulations. A10230-33 (Hearing Tr.). Apotex does not rely on that argument before this Court and cannot do so in its Reply brief. "Arguments raised for the first time in a reply brief are not properly before this court." *United States* v. *Ford Motor Co.*, 463 F.3d 1267, 1276 (Fed. Cir. 2006). *See also Novosteel Sa* v. *United States,* 284 F.3d 1261, 1274 (Fed. Cir. 2002). In any event, there was no evidence whatsoever that a POSA would have believed a bulking agent was useful in preparing a tigecycline composition.

e. It Was Not Legal Error for the Board to Consider and Reject Apotex's Motivation Argument.

What Apotex has is a factual dispute with the Board—whether the prior art would have motivated a POSA to combine tigecycline with lactose at the specific pH and molar ratio ranges—but it cannot be legal error for the Board to consider and reject Apotex's factual arguments. Thus, Apotex's own focus on epimerization renders this case distinguishable from *Senju Pharm. Co.* v. *Lupin Ltd.*, 780 F.3d 1337 (Fed. Cir. 2015) in a number of respects. There, the challenger identified a motivation to substitute gatifloxacin into pharmaceutical compositions that used other quinolones. The district court found that argument factually persuasive. In stark contrast to the Board in this case, after considering multiple prior art compositions, including commercialized products, the district court in *Senju* made the factual finding that "the prior art reveals that disodium edetate is a conventional excipient with beneficial properties used in [the specific types of pharmaceutical compositions at issue]." *Senju Pharm. Co.* v. *Apotex, Inc.*, 717 F. Supp. 2d 404, 421 (D. Del. 2010). *See also Senju Pharm. Co.* v. *Lupin Ltd.*, 2013 U.S. Dist. Lexis 112439, *33-34 (D. Del. Aug. 9, 2013) ("adopt[ing] its previous analysis of the use of gatifloxacin and EDTA" from *Senju Pharm.*, 717 F. Supp. 2d at 421). In this case, however, lactose was not a conventional excipient in tetracycline compositions. The question at issue before the Board was whether there was a reason to use tigecycline in place of minocycline **in the particular**

compositions disclosed in CN '550, rather than preparing tigecycline compositions according to any of the numerous other prior art minocycline or tetracycline compositions that (in contrast to CN '550) explicitly disclose their chemical and epimeric stability, but do not use lactose. *See* A1673-75, A1754-58 (Mitscher Decl.) (discussing prior solutions to the epimerization of tetracyclines found in the literature that explicitly state that they address the epimerization of tetracyclines, including A654-63 (Moreno-Cerezo), A232-37 (U.S. Patent No. 5,122,519), and A2665-80 (U.S. Patent No. 4,701,320)); A1680-81 (Mitscher Decl.) (discussing prior art references that make statements about the stability of compositions containing tetracyclines, including A2489-94 (U.S. Patent No. 4,418,060 at 3:10-40), A2495-98 (U.S. Patent No. 4,081,528 at 1:65-2:10, 2:56-60), A2662-64 (U.S. Patent No. 3,026,248 at 1:11-55, 2:32-71), A2499-06 (U.S. Patent No. 4,376,118 at 1:1-2, 1:54-2:25), A238 (U.S. Patent No. 3,106,512 at 1:35-37), A272-82 (Kreilgard at 1090), A292-296 (Pastia at 458), A300-20 (Lawter at 2:1-8, 6:24)). Apotex answered that question by asserting that CN '550 offered a solution to the problem of epimeric stability, *see supra* p. 9-15. The Board found Apotex's arguments unpersuasive, but it was not error for the Board to have considered that very problem.

Apotex's reliance on *Alcon Research, Ltd.* v. *Apotex Inc.*, 687 F.3d 1362 (Fed. Cir. 2012), is equally misplaced. There, the prior art established two actual

reasons why a skilled artisan might have wanted to use olopatadine in an eye drop formulation—as an antihistamine or as a mast cell stabilizer. *Id.* at 1365, 1368-69. This Court simply noted that either motivation in the field could suffice to establish the obviousness of the claimed invention, and that the analysis need not focus on the one that had motivated the inventors. *Id.* at 1368-69. That is a far cry from this case, where the only reason or motivation advanced as to why a POSA would use lactose with tigecycline was to develop a formulation that would be stable against epimerization. On this record, it was entirely correct for the Board to evaluate whether CN '550 in fact offered a solution to that problem. Put simply, like the Willie Sutton theory of bank robbery,[6] the Board addressed epimerization because that's where the arguments were.

2. None of the Alternative Motivations Advanced by Apotex in its Brief Provide a Basis for Reversal.

Apotex argues that the Board failed to consider three additional motivations for combining the asserted prior art references. Br. 28-29. The Board did in fact consider one of the motivations in its Final Written Decision. The other two address the subsidiary issue of what pH a POSA would use, rather than the primary question of whether a POSA would have used lactose with tigecycline. These arguments cannot support either reversal of the Board's factual finding on that

[6] He robbed banks because that's where the money is.

determinative issue or the obviousness of the claimed invention.

a. Apotex's Structural Similarity Argument was Considered and Depends on its Rejected Epimerization Theory.

Apotex first claims that the Board erred by failing to consider its argument that the POSA would have been motivated to substitute minocycline in CN '550 with tigecycline based on the "structural similarity" of those compounds, "including the identity of their A and B rings and the fact that they undergo epimerization at the same C4 dimethylamino group by the same reaction." Br. 28. In fact, the Board considered this argument, recited the argument in its Final Decision, and found that this argument—even in combination with the other arguments that Apotex presented—was not sufficient to demonstrate that the claimed invention was obvious. The Board's Final Decision recognized explicitly that "Petitioner contends that a person skilled in the art 'would find reason to substitute tigecycline for minocycline in the lyophilized formulation of CN '550' . . . because minocycline and tigecycline are tetracycline antibiotics that have identical A and B rings, and undergo epimerization at the C4 dimethylamino group by the same reaction." A8-9, A13. Furthermore, the Board held that "Petitioner does not provide any evidence or explanation why a person having ordinary skill in the art would have expected reasonably that the substitution [of] tigecycline for minocycline in the CN '550 compositions would have resulted in a stabilized

tigecycline composition," thereby rejecting Apotex's arguments based on tigecycline's properties, including its alleged structural similarity to minocycline. A12 (Final Decision). Thus, the Board concluded as a factual matter that Apotex's arguments, including its argument relying on structural similarity, were unpersuasive.[7] Apotex is simply incorrect in stating that the Board failed to consider this argument.

Apotex's assertion to this Court that its structural similarity argument is distinct from the epimerization motivation is also refuted by Apotex's arguments below and even the very statement that presents the argument in its brief here. Apotex contends that the Board failed to consider that "Apotex argued that the structural similarity of tigecycline and minocycline, including the identity of their A and B rings and **the fact that they undergo epimerization at the same C4 dimethylamino group by the same reaction**, would have led a POSITA to

[7] Apotex, in essence, argues that the Board should have provided more explanation in rejecting the structural similarity argument. Br. 28. That argument is legally foreclosed. *Lowder* v. *Dep't of Homeland Sec.*, 504 F.3d 1378, 1383 (Fed. Cir. 2007) ("The failure to discuss particular contentions in a case, however, does not mean that the tribunal did not consider them in reaching its decision. … All that it means is that the author of the opinion, for whatever reasons, did not deem it necessary or appropriate specifically to discuss those points. The author of an opinion has broad discretion to determine what the opinion should contain and in what detail.") (citing *Hartman* v. *DVA*, 483 F.3d 1311, 1315 (Fed. Cir. 2007); *Charles G. Williams Constr., Inc.* v. *White*, 326 F.3d 1376, 1380 (Fed. Cir. 2003); *Carolina Tobacco Co.* v. *Bureau of Customs and Border Prot.*, 402 F.3d 1345, 1350 (Fed. Cir. 2005)).

substitute minocycline in CN '550 with tigecycline." Br. 28 (emphasis added). In other words, the structural similarity argument for substituting tigecycline for minocycline—that the similarity in the regions of the molecules where epimerization occurs would motivate a POSA to use lactose to stabilize tigecycline—is not independent of the contention that CN '550 teaches stabilization of minocycline; it is premised on that contention.

The Petition confirms this relationship between the alleged structural similarity of tigecycline to minocycline and the motivation argument based on the prior art's asserted epimeric stabilization of minocycline. The relevant portion of Apotex's Petition asserts that minocycline and tigecycline are "analogs" of one another that contain identical A and B rings, where epimerization occurs, and share the same mechanism of C4 epimerization. *See* A78, A85 (Petition). Apotex's Petition makes clear that the alleged structural similarity is only relevant if a POSA believes that CN '550 teaches that lactose prevents epimerization of minocycline, asserting: "A person of ordinary skill in the art would understand and expect that lactose would be **effective to stabilize minocycline and tigecycline against C4 epimerization** in a solution having a pH from 0.1-7.5, including an acid pH of 2.0-3.5, as taught by CN '550, based on the exact structural identity of the A and B rings in these analogs." A78 (Petition) (citing A161-162 (Nelson Decl.)) (emphasis added).

Likewise, Apotex cites to the argument in its Petition that the claimed invention required only the "simple substitution of tigecycline for its **known analog** minocycline in the prior art CN '550 composition." Br. 28; A85 (Petition) (emphasis added). But again, Apotex's Petition asserted that the relevance of tigecycline being an alleged "analog" of minocycline was that a POSA "would recognize [that the] technique for stabilizing minocycline disclosed in CN '550 by using lactose, would similarly stabilize and improve a composition containing the analog antibiotic tigecycline." A85 (Petition). Thus, this argument, too, was premised on the assertion that the POSA would have looked to CN '550 for potential solutions to the problem of epimeric stability and, having found a solution that applied to minocycline, would have applied that solution to the allegedly structurally similar analog tigecycline. Because the Board disagreed with the premise for that argument—and concluded that CN '550 did not, in fact, offer a solution to the problem of epimeric stability, A15-22 (Final Decision)—there would have been no reason for the POSA to substitute tigecycline for minocycline in the compositions of CN '550.[8]

[8] Apotex's argument is factually baseless in any event. Wyeth's expert Dr. Mitscher explained that "epimerization is triggered (and thus inhibited) by different chemical reactions depending on the particular structure of the molecule that is epimerizing." A1663 (Mitscher Decl.). Thus, he concluded, "[e]pimerization usually calls for a solution unique to a particular molecule or chemical structure." A1664; *see also* A1673. Apotex's expert did not rebut that testimony, but simply offered the exact same conclusory statements quoted above

The Board recognized that Apotex's arguments regarding the properties of tigecycline, including "the exact structural identify of the A and B rings in" minocycline and tigecycline, depended on a finding that the prior art disclosed that lactose stabilized minocycline. A13 (Final Decision). In rejecting these arguments, the Board explained that Apotex's "contentions in this regard are insufficient because they presume that a person of ordinary skill in the art would have recognized that the compositions disclosed in CN '550 were stable against epimerization." *Id.* The Board thus rejected the premise of Apotex's argument in an unchallenged factual finding. A9-22 (Final Decision). The notion that Apotex's argument was "never addressed by the Board," Br. 28, mischaracterizes both Apotex's argument below and the Board's explicit consideration and rejection of it.

3. Neither of Apotex's pH-Related Motivations Renders the Claimed Compositions Obvious.

Apotex also faults the Board for allegedly ignoring its second and third motivations to combine the asserted prior art references to arrive at the pH ranges recited in the dependent claims of the '828 patent. Br. 29. Neither of these

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from the Petition, with no additional explanation for why the supposed structural similarity between the two compounds would have motivated the POSA to substitute one for the other with a reasonable expectation of success in doing so. *See* A161-62, 168 (Nelson Decl.). Thus, even setting aside the Board's unchallenged interpretation of the prior art, it could not have ruled in Apotex's favor on this issue.

motivations would render the claims obvious; they relate only to the pH limitations. The second argument is based expressly on chemical stability concerns, including specifically epimerization, about which Apotex does not challenge the Board's findings. And the final motivation was not part of the Ground upon which trial was instituted, was not argued at trial, and is therefore not properly part of this appeal.

a. Apotex's Motivation Arguments Regarding pH Ranges Cannot Render the Claims Obvious in View of the Board's Unchallenged Factual Findings.

As an initial matter, Apotex's arguments that a POSA would be motivated to arrive at the pH ranges of the dependent claims either by combining the CN '550, Pawelczyk, and Naggar references (its second argument) or by using conventional injection solutions (its third argument) are legally and logically insufficient to support reversal. The arguments are addressed explicitly to the pH limitations of the dependent claims, rather than the distinct limitations requiring tigecycline and lactose. Br. 29. They simply do not bear on the dispositive question of whether it would have been obvious to prepare the claimed tigecycline compositions using lactose, on which the Board made factual findings that Apotex does not dispute were supported by substantial evidence. A9-22 (Final Decision).

In other words, even if the POSA were motivated to use the claimed pH range, as Apotex asserts, the failure of the references to disclose tigecycline, or

motivate a POSA to substitute tigecycline for minocycline, is fatal to Apotex's argument.[9] A10 ("As discussed in more detail below, none of CN '550, Pawelczyk, or Naggar discloses or discusses tigecycline."); A12 ("Petitioner does not provide any evidence or explanation why a person having ordinary skill in the art would have expected reasonably that the substitution [of] tigecycline for minocycline in the CN '550 compositions would have resulted in a stabilized tigecycline composition."); A14 ("We are not persuaded, however, that Petitioner has established that a person having ordinary skill in the art would have found it obvious to substitute tigecycline for minocycline in the composition disclosed in CN '550."). Accordingly, these alleged motivations, even if credited, could not render the asserted claims of the '828 patent obvious without reversal of the Board's findings as to using lactose with tigecycline.

b. Apotex's Second Motivation Argument Depends on a Finding that the Prior Art Disclosed Epimeric Stability.

Moreover, like its argument regarding structural similarity, Apotex's second

[9] Pfizer and its experts discredited the pH arguments that Apotex presented in its Petition and raises again here. If, as Apotex suggests, the POSA sought to optimize the pH of a tigecycline composition to "control oxidative degradation," Br. 29, Dr. Mitscher explained that the POSA would have selected a pH of 3.6 or below, which is outside all but the broadest pH ranges in the claims of the '828 patent. *See* A1601-02 (Patent Owner Response). Neither Apotex nor its expert sought to refute this evidence, and Apotex's expert Dr. Nelson agreed that a POSA formulating tigecycline would not want to use a pH above 4.4 (outside the ranges of claims 10, 11, 16, 17, 22, and 23). A2042 at 307:2-16 (Nelson Depo.).

argument is premised on a motivation to prevent epimerization of tigecycline. As Apotex's own contentions recognize, without the motivation to reduce epimerization, there is simply no reason to look to the asserted references or to combine them to optimize CN '550's pH ranges. Apotex explicitly relies on the motivation of preventing epimerization to arrive at the pH ranges of the dependent claims, arguing that "Naggar teaches tetracyclines solutions having pH above 4 to control epimeric degradation." Br. 29. Far from stating an independent motivation that the Board failed to consider because of its focus on epimerization, Apotex's second argument is part and parcel of the epimerization rationale that the Board rejected.

c. Apotex's Reliance on pH Disclosures of Other References Improperly Challenges the Underlying Institution Decision Itself.

Apotex's third allegedly overlooked motivation—namely that the POSA would have arrived at the claimed pH ranges because those ranges were "commonly used in conventional injection solutions," Br. 29—was included in Apotex's Petition as part of Ground 1 asserting that CN '550 alone rendered the '828 patent claims obvious. *See* A81-82, A49 (Petition); *see also* A70-86 (Petition). Indeed, Apotex does not even try to obscure its attempted resuscitation of Ground 1 on appeal, arguing that "CN '550 itself renders obvious all or at least a substantial majority of the '828 patent claims." Br. 14. But the Board did not

institute review on that basis, and Apotex did not seek reconsideration of that decision. *See* A1019; Br. 1 (Statement of the Issues), 1-31. Nor does Apotex's appeal address the Board's decision to decline institution of Ground 1, let alone assert that it was erroneous or request reversal of the Institution Decision. Br. 1 (Statement of the Issues).[10]

Rather than seek reversal of the Institution Decision, Apotex attempts to ignore it and retrospectively merge non-instituted Ground 1 with instituted Ground 2. But the grounds were distinct: Apotex's Ground 1 argument regarding the recited pH ranges was that a POSA "could readily determine the suitable pH ranges for intravenous administration of a lyophilized composition containing tigecycline and lactose to a patient" based on the pHs of common injection solutions, including saline injection solution and dextrose injection solution. A81 (Petition). Its argument in Ground 2 relied exclusively on Naggar and Pawelczyk to assert the obviousness of the pH ranges claimed in the '828 patent. A86-90 (Petition). There was no reason for the Board to review the argument that a POSA would have used the claimed pH ranges based on common injection solutions because, aside from the fact that its findings regarding lactose and tigecycline

[10] Nor can Apotex assert error in the Institution Decision for the first time in its Reply Brief. *Ford Motor Co.*, 463 F.3d at 1276-77 ("Arguments raised for the first time in a reply brief are not properly before this court."); *Novosteel SA*, 284 F.3d at 1274.

rendered Apotex's pH arguments irrelevant, it was not part of the trial.[11] The notion that the Board erred by failing to address in its Final Written Decision arguments on which it declined to institute trial is simply untenable.

CONCLUSION

The judgment of the Board should be affirmed.

Respectfully submitted,

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[11] In any event, Apotex's argument suffers from a failure of proof. Though Apotex cites the pH of the injection solutions themselves, it offered no evidence whatsoever that a composition containing not only the injection solutions, but also tigecycline, lactose, and an acid (as the claims require), would have a pH within the claimed ranges. *See* A81-82 (Petition); A163-65 (Nelson Decl.).

CERTIFICATE OF SERVICE

I, David I. Berl, hereby certify that on January 25, 2016, I caused the foregoing document to be electronically filed with the Clerk of the Court using CM/ECF, which will send notification to the registered attorneys of record that the document has been filed and is available for viewing and downloading. Notice of such filings also will be sent to the below referenced persons via electronic mail:

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Upon acceptance by the Court of the e-filed document, six paper copies of the Brief will be filed with the Court within the time provided in the Court's rules. In addition, two copies of the Brief will be sent via Federal Express to Appellant's counsel, identified above, within that same time frame.

Dated: January 25, 2016

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CERTIFICATE OF COMPLIANCE
PURSUANT TO FED. R. APP. P. 32(a)(7)(C)

This brief complies with the type-volume limitation of Federal Rule of Appellate Procedure 32(a)(7)(B). The brief contains 12,074 words, excluding the parts of the brief exempted by Federal Rule of Appellate Procedure 32(a)(7)(B)(iii).

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Dated: January 25, 2016

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